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FACILE RETRO DIECKMANN REACTIONS OF 3-OXO-CARBAPENAM ESTERS

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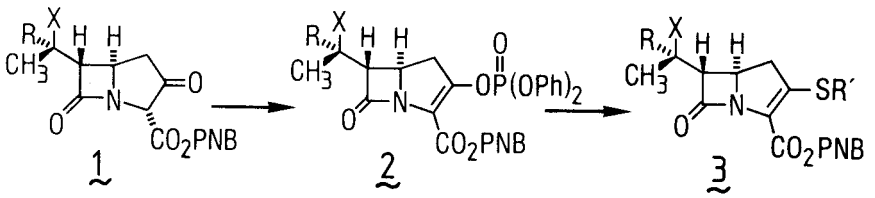
Abstract - Bicyclic ketones 1b and 1c reacted with nucleophiles to give azetidinones 4. Azetidinone 4a was deprotected to give 5, which was antibacterially inactive.

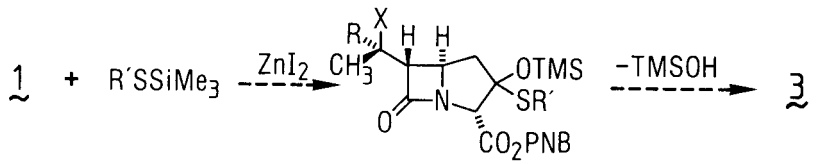
The bicyclic ketone 1a was developed by Merck chemists as a central intermediate for the derivation of carbapenem antibiotics[2]. After conversion to the appropriate enol derivative 2, preferably the diphenyl phosphoenolate, reaction with a suitable mercaptan under base catalysis gives the 3-thio substituted carbapenem ester 3 (Scheme 1). It occurred to us that a simpler way of achieving this conversion might be by reacting 1 with silylated mercaptans under mild Lewis acid catalysis[3] as depicted in Scheme 2.



1 2 3

a. R=H, X=OP (P=protective group)
b. R=H, X=F
c. R=CH3, X=F

Scheme 1



Scheme 2

In the event, reaction of 1c[4] with methyl trimethylsilyl sulfide catalyzed by dried ZnI_2 under a variety of conditions was unsuccessful. On the other hand, catalysis by KF/18-crown-6 resulted in a fast and clean reaction at room temperature. However, the product of this reaction was not the hoped for carbapenem ester 3 as was immediately clear from its UV-spectrum lacking the characteristic maximum around 290-300 nm[5]. The ß-lactam absorption in the IR at 1754 cm^{-1} rather suggested a monocyclic ß-lactam; an additional absorption at 1680 cm^{-1} pointed towards a thiol ester. The presence of two diastereotropic protons with a relatively high J_{AB} of 18 Hz in the proton NMR, together with a molecular ion of 412 in the mass spectrum unequivocally establishes structure 4a for this product.

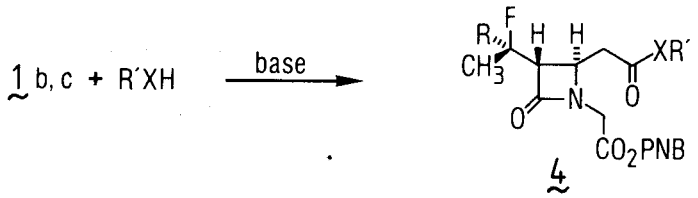
It appears that the more electrophilic site in this highly strained bicyclic system is the ketone moiety, rather than the ß-lactam carbonyl[6]. To establish the generality of this observation we reacted ketones 1a and b with some assorted nucleophiles (Scheme 3, see Table for details).

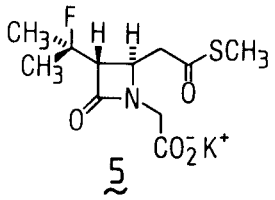
Table. Reactions of bicyclic ketones 1b and 1c with nucleophiles

Entry	Starting material + 4	Nucleophile	Conditions	Product mp °C	Yield++
1.	1c	$MeSSiMe_3$, cat. KF, 18-c-6	CH_2Cl_2, RT 3.5 h	4a, oil	64 %
2.	1b	$MeSSiMe_3$ cat. KF, 18-c-6	CH_2Cl_2, RT 3.5 h	4b, oil	77 %
3.	1b	EtOH, cat. pyridine	$EtOH/CH_2Cl_2$ 1:1, RT, 16 h	4c, oil	83 %
4.	1c	$PhCH_2NH_2$	CH_2Cl_2, RT, 1 h	4d, oil	55 %
5.	1b	$PhCH_2NH_2$	CH_2Cl_2, RT, 0.5 h	4e, 75-78°	87 %
6.	1b	CH_3NO_2, KO^tBu	CH_3NO_2, RT 16 h	4f, 145-147°	42 %

+ All compounds are racemic mixtures.

++ Yields of chromatographed (silica) products.





a. $R = CH_3$, $XR' = SCH_3$
b. $R = H$, $XR' = SCH_3$
c. $R = H$, $XR' = OEt$
d. $R = CH_3$, $XR' = NHCH_2Ph$
e. $R = H$, $XR' = NHCH_2Ph$
f. $R = H$, $XR' = CH_2NO_2$

Scheme 3

Reaction with benzylamine was rapid and led to the azetidinone amides 4d and 4e[7]. Reaction of 1b with ethanol catalyzed by a small amount of pyridine proceeded overnight and gave the azetidinone ester 4c. A carbon nucleophile was found in the potassium salt of nitromethane, which reacted overnight with 1b to give nitroketone azetidinone 4f in moderate yield.

Not much is known about the biological activity of monocyclic ß-lactams having an acetic acid group on nitrogen as recognition site; closest analogues are the nocardicins and they are only moderately active antibacterials[8]. A second detrimental factor is the carbapenem type side chain in the 3-position: N-sulfonated monobactams with such side chains were shown to be devoid of antibacterial activity[9]. Nonetheless, we subjected azetidinone 4a to catalytic hydrogenation (H_2, Pd/C, EtOAc-phosphate buffer pH 7 1:1, 3.5 h) to obtain potassium salt 5 in 36 % yield after RP-18 chromatography (H_2O) and lyophilization of the relevant fractions. As expected the compound did not show any appreciable antibacterial activity (MIC >50 µg/ml in serial dilution test) against a range of gram-positive and gram-negative bacteria, and was a poor ß-lactamase inhibitor.

In contrast with the above we found that stabilized phosphoranes react with bicyclic ketone 1 to give C-3 carbon substituted carbapenem esters as a mixture of isomers (endo- and exocyclic double bond at C-3)[10].

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7. Spectral Data (^{1}H and ^{13}C NMR spectra in $CDCl_3$, except 5 (D_2O); IR spectra in CH_2Cl_2): 4a: ^{1}H NMR: δ 8.24 and 7.55 (4H, AA'BB', J = 9.0 Hz, Ar), 5.27 (2H, s, CH_2Ar), 4.23 (1H, ddd, J = 7.7, 4.8, 2.5 Hz, H-4), 4.24 and 4.03 (2H, AB-q, J = 18.0 Hz, NCH_2), 3.09 (1H, dd, J = 20.0, 2.5 Hz, H-3), 3.04 and 2.99 (2H, ABX, J_{AB} = 16.2 Hz, J = 7.7, 4.8 Hz, CH_2COS), 2.28 (3H, s, SCH_3), 1.53 (3H, d, J = 21.5 Hz, CH_3), 1.43 (3H, d, J = 21.5 Hz, CH_3). ^{13}C NMR: δ 11.7 (SCH_3), 23.89 (CH_3, J_{CF} = 24.3 Hz), 26.60 (CH_3, J_{CF} = 24.1 Hz), 42.43 (CH_2COS), 47.24 (NCH_2), 51.81 (C-4), 64.51 (C-3, J_{CF} = 24.3 Hz), 65.56 (OCH_2), 92.71 (CF, J_{CF} = 169.3 Hz), 123.85, 128.85, 142.4, 144.9 (PNB), 165.67 (C-2, J_{CF} = 9.0 HZ), 167.96 (CO_2), 197.18 (COS). IR: 1754, 1680 cm^{-1}. UV (CH_3OH) λ max: 263 (3 700), 238 (ε 2900), 224 (ε 2400) nm. 4c: ^{1}H NMR: δ 8.24 and 7.54 (4H, AA'BB', J = 9.0 Hz, Ar), 5.26 (2H, s, CH_2Ar), 4.97 (1H, ddq, J = 48.5, 7.2, 5.9 Hz, CF), 4.24 and 4.12 (2H, AB-q, J = 18.0 Hz, NCH_2), 4.18 (1H, ddd, J = 8.5, 4.7, 2.4 Hz, H-4), 4.10 and 4.09 (2H, 2 q, J = 7.2 Hz, CH_2CH_3), 3.08 (1H, ddd, J = 18.0, 7.3, 2.4 Hz, H-3), 2.82 and 2.76 (2H, ABX, J_{AB} = 17.2 Hz, J = 8.5, 4.7 Hz, CCH_2CO_2), 1.48 (3H, dd, J = 24.3, 5.9 Hz, $CFCH_3$), 1.24 (3H, t, J = 7.2 Hz, CH_2CH_3). IR: 1767, 1734 cm^{-1}. 4e: ^{1}H NMR: δ 8.20 and 7.50 (4H, AA'BB', J = 9.0 Hz, $ArNO_2$), 7.22-7.37 (5H, m, Ph), 5.93 (1H, br t, J = 5.5 Hz, NH), 5.18 and 5.20 (2H, AB-q, J = 13.4 Hz, CO_2CH_2), 4.96 (1H, ddq, J = 48.1, 7.5, 6.5 Hz, CF), 4.39 (2H, d, J = 5.5 Hz, $NHCH_2$), 4.24 (1H, ddd, J = 8.3, 4.3, 2.3 Hz, H-4), 4.21 (2H, s, NCH_2CO_2), 3.06 (1H, ddd, J = 17.3, 7.5, 2.3 Hz, H-3), 2.76 and 2.69 (2H, ABX, J_{AB} = 15.5 Hz, J = 8.3, 4.3 Hz, CH_2CON), 1.47 (3H, dd, J = 24.4, 6.5 Hz, CH_3). IR: 1765, 1677 cm^{-1}. 4f: ^{1}H NMR: δ 8.24 and 7.54 (4H, AA'BB', J = 9.0 Hz, Ar), 5.53 and 5.47 (2H, AB-q, J = 17.5 Hz, CH_2Ar), 5.26 (2H, s, CH_2NO_2), 4.98 (1H, ddq, J = 48.4, 7.0, 6.5 Hz, CF), 4.30 and 4.02 (2H, AB-q, J = 18.1 Hz, NCH_2CO_2), 4.26 (1H, ddd, J = 7.5, 5.5, 2.3 Hz, H-4), 3.12-3.19 (2H, m, CH_2COC), 3.12 (1H, ddd, J = 19.2, 7.0, 2.3 Hz, H-3), 1.46 (3H, dd, J = 23.3, 6.5 Hz, CH_3). IR: 1769, 1751 cm^{-1}. 5: ^{1}H NMR: δ 4.23 (1H, ddd, J = 7.2, 5.9, 2.3 Hz, H-4), 3.83 (2H, s, CH_2COS), 3.37 (1H, dd, J = 24.2, 2.3 Hz, H-3), 3.22 and 3.08 (2H, ABX, J_{AB} = 15.6 Hz, J = 7.2, 5.9 Hz, CH_2COS), 1.52 (3H, d, J = 20.6 Hz, CH_3), 1.43 (3H, d, J = 20.6 Hz, CH_3). IR (KBr): 1732, 1669 cm^{-1}. UV (H_2O) λ max: 234 (ε 1400), 218 (ε 900) nm.
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